Remarks

Upon entry of this amendment, claims 1-3, 6, 22, 24, 27-28, 30 and 35-39 will be pending in this application.

Claims 1, 2, 6 and 37 are being amended to more particularly define the moieties X and Y. Claims 35 and 38 are being amended to clarify that R^{10} and R^{11} are independently chosen from the specified groups. Claims 6, 30, and 37 are further amended to put the claims in a form consistent with US practice (i.e., "and", "or", "a"). Support for these amendments is found in the claims as originally filed. Other amendments are being made and supported as described below. No new matter is added.

All amendments are made without prejudice. Applicants reserve the right to pursue any canceled subject matter, and any subject matter supported by the specification, in a continuing application.

Claim Rejections – 35 USC 112 – 2nd paragraph

Claims 1-3, 6, 22, 24, 27, 28, 30, 31, 33 and 35-39 are rejected under 35 USC 112, 2nd paragraph. The Examiner asserts that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

1. the term "substituted" without saying which substituents are intended is said by the Examiner to be indefinite.

Applicants have defined suitable substituents for substituted alkyl, alkoxy, aryl, heteroaryl, aralkyl, heteroaralkyl, 3- to 7- membered carbocyclic ring, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkyloxycarbonyl, heteroaralkyloxycarbonyl, aralkylcarbonyl, heteroaralkylcarbonyl, and alkylene. See pages 14-16 and 19 of the specification. Applicants respectfully submit that one skilled in the art would understand the scope of the term "substituted".

2. the term "heteroaryl" is said by the Examiner to be indefinite "because it is not known how many atoms are present, how many and what kind of heteroatoms are involved, what size ring is intended and how many rings are present".

The claims as presently amended expressly recite a definition for the term "heteroaryl". Support for this amendment is found on page 12, lines 22-28 of the specification. This definition includes the number of atoms, number and kind of heteratoms, and the size and number of rings.

3. the term "carbocyclic" is said by the Examiner to be indefinite "because it is not known what kind of a ring is intended..."

Applicants respectfully submit that the term "carbocyclic" would be understood by those skilled in the art. In particular, the present claims recite "3- to 7- membered carbocyclic ring". One skilled in the art would understand this to mean a monocyclic moiety containing 3 to 7 carbon ring atoms, in which all of the ring atoms are carbon (in contrast to "heterocyclic", which can contain a non-C ring atom). One skilled in the art would understand that a carbocyclic ring could be spiro (e.g., the ring includes the carbon to which R^5 and $R^{5'}$ are attached), and could be saturated, unsaturated, or bridged.

4. the phrase "pharmaceutically acceptable derivatives" is said by the Examiner to be indefinite "because one skilled in the art cannot say what derivative is intended".

Solely to advance prosecution, Applicants have amended the present claims to replace the term "derivative" with "salt". Support for this amendment is found on pages 16-17 of the specification.

5. The Examiner asserts that the nature of the additional ingredients in claim 28 is not known.

Applicants have amended claim 28 to expressly recite that the taxane, vinca alkaloid and topoisomerase I inhibitors are anti-cancer agents. Such agents are well known in the art. See, e.g., Denny, W.A. et al., *Current Topics in Medicinal Chemistry* 2003, *3*, 339-353 and Abal, M. et al., *Current Cancer Drug Targets,* 2003, *3*, 193-203, copies of which are enclosed.

6. The Examiner posits that claims 1 and 28 are not so linked as to form a single inventive concept.

Claim 28 is directed to a composition comprising a pharmaceutically acceptable excipient, a compound of claim 2, and an anti-cancer agent selected from taxanes, vinca

alkaloids and topoisomerase I inhibitors. Claim 28 depends (indirectly) from claim 2, which is directed to compounds represented by formula II and pharmaceutically acceptable salts thereof.

Claim 1 is directed to compounds represented by formula I and pharmaceutically acceptable salts thereof. Formula I is within the scope of Formula II recited in claim 2. Therefore, claims 1 and 28 are linked through the structure of claim 2.

Reconsideration and withdrawal of the rejections under 35 USC 112, 2nd paragraph is respectfully requested.

Claim Rejections – 35 USC 112 – 1st paragraph

1. Claims 1-3, 6, 22, 24, 27, 28, 30, 31, 33 and 35-39 are rejected under 35 USC 112, 1st paragraph, because according the Examiner the specification does not reasonably provide enablement for solvates of the compound of formula I.

Solely to advance prosecution Applicants have amended the claims to remove the term "solvates". Since solvates are a form species of the presently claimed compounds and salts, the present claims nonetheless encompass such forms.

2. On page 3 of the Office Action, Claims 1-3, 6, 22, 27, 28, 30, 31, 33 and 35-39 are rejected under 35 USC 112, 1st paragraph, because according to the Examiner the specification does not reasonably provide enablement for using the compounds of claim 2. The Examiner posits that the specification is not adequately enabled for the scope of fused rings that have diverse atoms at A, B, D and E and differing ring systems fused to the pyrimidinone, and that compounds made and tested represent the scope of claim 24, and not claim 2. On pages 3-5 of the Office Action, the Examiner sets forth details regarding the bases of the rejection. Applicants respectfully traverse.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See, e.g., *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). See also *In re Wands*, 858 F.2d at 737, 8USPQ2d at 1404 (Fed. Cir. 1988).

A patent need not teach, and preferably omits, what is well known in the art. See, e.g., *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. See, e.g., *In re Certain Limited-Charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Further, an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. See, e.g., *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). A considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. See, e.g., *In re Wands,* 858 F.2d 731, 737m 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Compliance with the enablement requirement does not turn on whether an example is disclosed. Indeed, the specification need not contain an example if the invention is otherwise disclosed in a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. See, e.g., *In re Borkowski,* 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright,* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also MPEP 2164.01, pages 2100-197 to 2100-198, Rev. 3, Aug 2005.

Preliminarily, Applicants note that the Examiner bases the rejection on the scope of formula II, particularly the scope of the fused rings with "...diverse atoms at A, B, D and E and differing ring systems fused to the pyrimidinone." However, claims 1 and 37-39 each have a benzene core ring "fused to the pyrimidinone ring", i.e., they lack the ring diversity objected to by the Examiner.

Applicants have provided sufficient direction regarding how to make and use compounds of the present invention.

First, Applicants have set forth a detailed description of suitable moieties in Formula I and II, including particular embodiments which would provide guidance to those skilled in the art regarding the direction in which experimentation should proceed. See, e.g., pages 8-22.

In addition, Applicants have set forth a detailed disclosure of how to prepare compounds of Formula I and II, including general schemes and working examples. See pages 38-55. The schemes include methods of making quinazolinones substituted with a diazepanone group (Schemes 1A, 1B, 2) and pyrido-pyrimidinones, pyrimido-pyridazinones, pteridinones, and pyrimido-pyrimidinones substituted with a diazepanone group (Schemes 3, 3a). Working examples 1-8 illustrate the preparation of quinazolinones substituted with a diazepanone group.

Applicants also disclose how to use the compounds of the invention, including in methods of inhibiting KSP or treating diseases of proliferating cells, such as cancer (see, e.g., pages 23-37 and working examples 9 and 11 at pages 55-58).

On page 3 the Examiner posits that determining the activity of compounds within Applicants' claimed scope would require synthesis of the substrate and testing them with Applicants' ATPase assay, and that this would be a large quantity of experimentation.

As stated above, Applicants have set forth a detailed disclosure of how to prepare compounds of Formula I and II. Those skilled in the art would be able to synthesize the compounds of Applicants' claims in light of this teaching and knowledge in the art. In addition, the fact that experimentation may be complex or time consuming does not necessarily make it undue. Applicants submit that synthesis and assay testing of chemical compounds is typically done by medicinal chemists and biologists. Assay testing such as described in the specification is routine. Furthermore, the specification provides a reasonable amount of guidance in the form of various particular embodiments of Formulas I and II, including synthetic schemes and specific examples. Indeed, the Examiner admits that Applicants provide synthetic guidance in Scheme 3a (page 43). Accordingly, preparation and testing of compounds of Formula I and II is not undue.

On page 4 of the Office Action, the Examiner posits that the nature of the invention requires an understanding of the KSP binding activity of small ligands and the ability of those compounds to inhibit KSP. The Examiner further states that detailed knowledge of the receptor is lacking, that no X-ray structure of the receptor is known, and that structural requirements of ligands to this receptor are poorly understood.

In fact, the crystal structure of KSP is known. Applicants direct the Examiner to Turner, J. et al., *J Bio Chem* 2001, *276*, 27, 25496-25502 (enclosed), which shows the crystal structure of the mitotic kinesin Eg5 (i.e., KSP).

Applicants submit that a person skilled in the relevant art includes medicinal chemists. Medicinal chemists are trained in the structure-based design of

pharmaceutical compounds for binding to particular biological targets. While testing would be required, such an artisan would be aware of known crystal structures and of how structural changes, e.g., changes to a heterocyclic ring, might affect biological activity.

On pages 4-5 of the Office Action, the Examiner asserts that "there is no reasonable basis for the assumption that the myriad of compounds embraced [by] the present formula (II) will all share the same biological properties", specifically noting rings which include N or S (thiophene). The Examiner goes on to say that the "diverse claimed fused heteroaryl rings are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity." The Examiner continues in the same vein on page 5, asserting that a skilled physician would question the inclusion of such fused rings, commensurate in scope with the claims, and that "the various heterocyclic radicals are not art-recognized as equivalent".

Applicants respectfully submit that the chemical literature supports the scope of the present claims. Examples from the chemical literature indicate that compounds having isosteric diversity may exhibit similar activity. For example, Wermouth, C.G., The Practice of Medicinal Chemistry, *Academic Press,* 1996, 206-215 describes isosteric replacements for various rings, including benzene, thiophene, pyridine, thiazole, and pyrazine. WO 03/049679 shows, *inter alia,* the use of diverse heterocyclic rings (pyrrole, pyrazole, oxazole, and thiazole rings) fused to a pyrimidinone in mitotic kinesin inhibitor compounds. WO 04/078758 also shows a diversity of heterocyclic rings (isothiazole and isooxazole rings) fused to a pyrimidone in cell-cycle inhibitors (the priority date of this reference is on or before 10/24/03, and evidences a level of skill in the art as of that time). Copies of these documents are enclosed.

In spite of Applicants' teachings and the state of the art, the Examiner limits the scope of enablement to Applicants' working examples (Office Action page 3, 5). However, the first paragraph of 35 USC 112 does not require specific exemplification of all of the subject matter falling within the scope of a broad claim term. See *In re Robins,* 166 USPQ 552, 555 (CCPA 1970); *In re Borkowski,* 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). The claims should not be limited to the compounds specifically exemplified in the specification when, as here, there is a clear disclosure and enablement of a broad genus.

Applicants respectfully submit that the Office has failed to meet its initial burden to establish a reasonable basis to question the enablement of the present claims. Furthermore, Applicants have rebutted the bases set forth by the Office for the rejection. Applicants respectfully submit that one skilled in the art could make and use the claimed invention without undue experimentation. Applicants respectfully request reconsideration and withdrawal of the rejection.

3. On page 6 of the Office Action, Claim 30 is rejected under 35 USC 112, 1st paragraph, as failing to comply with the enablement requirement. The Examiner asserts that the claim reads on KSP inhibition *in vitro*, and in mammals with below normal KSP activity, normal KSP activity, or asymptomatic mammals with up-regulated KSP activity. The Examiner posits that the specification fails to teach any benefit to be gained from such actions, and questions whether extensive experimentation is required to determine if a use falls within the claim.

Applicants respectfully submit that those skilled in the art would understand that a method of inhibiting KSP would be useful both *in vitro* and *in vivo* (in experimental animal models utilizing abnormally high KSP expression and in mammals with abnormally high KSP expression related to disease conditions, such as described in the specification at pages 27-29). One skilled in the art would also understand how to determine if KSP inhibition occurred.

As discussed in the specification, the perturbation of mitotic kinesin function causes malformation or dysfunction of the mitotic spindle, frequently resulting in cell cycle arrest and cell death. Applicants also state that other known anti-cancer agents, e.g., taxanes and vinca alkaloids, are known to act on the mitotic spindle (via the microtubules), and it is presumed that disruption of the mitotic spindle results in inhibition of cancer cell division and induction of cancer cell death. Therefore, Applicants disclose that mitotic kinesins are attractive targets for new anti-cancer agents. See, e.g., pages 1-3 and 6-7. See also Mayer, T.U. et al., *Science*, 1999, *286*, 971-974; and Kapoor, T.M. et al., *J. Cell Biol.*, 2000, *150, 5*, 975-988 (copies enclosed). For example, Mayer et al. show that a small molecule (monastrol) which specifically inhibited the motility of Eg5, arrested mammalian cells in mitosis with monopolar spindles (page 971). Mayer et al. conclude that because compounds that cause mitotic arrests by other mechanisms have shown antitumor activity in humans, monastrol may serve as a lead for the development of anticancer drugs (page 974).

As described in the specification (page 26, lines 17-20), microscopic methods for monitoring spindle formation and malformation are well known. In particular, the specification cites to Whitehead, C.M. et al., *Journal of Cell Science,* 1998, *111,* 2551-2561 and Gaglio, T. et al., *The Journal of Cell Biology,* 1996, *135, 2,* 399-414, copies of which are enclosed. In particular, it has been shown that Eg5 inhibition is characterized by monopolar spindle formation. See for example, Whitehead et al., page 2552-2553 ("Results"). See also Applicants' Example 9, which describes an assay for determining monopolar spindle formation.

It would be appreciated by the skilled artisan that mitotic arrest and spindle formation and malformation can be monitored microscopically in cell culture or by biopsy of mammalian tissue. In particular, the phenotype of monopolar spindle formation associated with KSP inhibition can be monitored microscopically, by methods known in the art and/or described in Applicants' specification.

One skilled in the art could readily determine the biochemical activity of compounds using known assays. In particular, the skilled artisan could determine the activity of compounds in inhibiting KSP (see, e.g., Applicants' example 10) as well as other proteins involved in mitosis. From this data the skilled artisan can determine the selectivity of a compound for inhibiting KSP. In the cellular context, one skilled in the art could determine whether there is an increase in the number of mitotically arrested cells (over baseline) and whether monopolar spindles are formed after exposure to compound concentrations similar to those showing biochemical inhibitory activity (one skilled in the art would understand that the determination of mitotic arrest and monopolar spindle formation should be done within about 12-24 hours of administration, so as to see the cell arrest in the cell cycle, which is about 24 hours). Similarly, one skilled in the art can determine *in vivo* whether there is an increase in the number of mitotically arrested cells (over baseline), and the formation of monopolar spindles after exposure to the compound. Such KSP-selective biochemical data and *in vitro* or *in vivo* cellular data would be reasonably indicative of KSP inhibition in the *in vitro* or *in vivo* cellular context.

Such KSP inhibition would be useful as an indicator of potential treatments for cell proliferation diseases, such as cancer.

While biochemical, *in vitro* cell, and *in vivo* assays would require experimentation, such experimentation is routinely done by biologists. Accordingly, it would not be undue.

Reconsideration and withdrawal of the rejection in view of the above remarks is respectfully requested.

4. Claims 31 and 33 are rejected under 35 USC 112, 1st paragraph, because according to the Examiner the specification does not reasonably provide enablement for treating diseases embraced by those claims.

Applicants have canceled claims 31 and 33 without prejudice, such that the rejection is moot.

Conclusion:

Applicants have addressed each of the rejections made by the Examiner. If any matters remain to be resolved before allowance, or discussion of any matter will facilitate the prosecution of this application, the Examiner is encouraged to call the undersigned attorney at the number provided below.

Respectfully submitted,

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